C. REMARKS

The claims have been amended in order to place the application in better form.

Claims 1, 4, 12, and 17 have been amended. The fact that Claims 1, 4, 12, and 17 have been amended is not to be construed as an admission by Applicants or Applicants' attorneys that such claims, prior to the amendment thereof, were unpatentable.

Claims 1, 2, 4, 10, and 12 - 21 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to point out particularly and claim distinctly the subject matter which Applicants regard as the invention. This rejection is respectfully traversed.

Claims 1, 4, 12, and 17 have been amended in order to add steps in accordance with the Examiner's helpful suggestions. The amendments of such claims, however, is not to be construed as an admission by Applicants or Applicants' attorneys that such claims, prior to the amendment thereof, were unpatentable.

The Examiner has taken the position that Claims 1, 4, 12, and 17 are unclear in that the Examiner believes that it is not clear how the administration of MSCs by any route would produce cardiomyocytes or promote angiogenesis limited to the heart of an individual.

In response, Applicants assert that, at Pages 3, 8, and 9 of the specification, it is stated that the mesenchymal stem cells can be administered by a variety of procedures, which include localized administration, i.e., direct administration to the heart, or by systemic administration, including intravenous administration. In addition, the Lee article, cited by the Examiner in the Office Action, at Page 729, column 2, lines 26 - 28,

states that "Transplanted stem cells also undergo a "homing" process in which they are attracted to the site of injury [citation]." Those skilled in the art, when reading the specification, would understand readily that, if administered systemically, the mesenchymal stem cells will travel to the heart in order to produce cardiomyocytes or blood vessels of the heart, thereby improving ventricular wall motion, repairing or regenerating blood vessels, or stimulating or promoting angiogenesis in the heart. Therefore, for the above reasons and others, the claims point out particularly and claim distinctly the subject matter Applicants regard as their invention, and it is therefore respectfully requested that the rejection under 35 U.S.C. 112, second paragraph, be reconsidered and withdrawn.

Claims 12 - 21 stand rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for a method of repairing or regenerating blood vessels, or a method of stimulating or promoting angiogenesis. This rejection is respectfully traversed.

The Examiner has taken the position that the specification does not provide an enabling disclosure for methods of repairing or regenerating blood vessels or stimulating or promoting angiogenesis in the heart of an individual by administering to the individual an effective amount of mesenchymal stem cells (MSCs). The Examiner also states that while the specification discloses that MSCs were identified surrounding and associated with the smooth muscle layer of blood vessels (Example 7, Page 20), it remains unknown whether the MSCs contributed to the formation of the blood vessels, as blood vessels already were present in the infracted pig heart.

Applicants assert that the examples do in fact show that MSCs did contribute to the formation of blood vessels in the heart.

In Example 6, a pig was subjected to a 60 minute LAD occlusion to produce an infarction. After the infarction, the pig was given DAPI-labeled allogeneic MSCs. The MSCs were administered to the left ventricular wall by endocardial catheter. Eight weeks after administration of the MSCs, MSCs were found surrounding, and associated with, blood vessels of the heart. The MSCs were localized within a blood vessel, and associated with the smooth muscle layer of the vessel. Thus, the MSCs are involved in the repair or regeneration of blood vessels of the heart.

In Example 7, a pig was subjected to an LAD occlusion to produce an infarction. Three days later, the pig was given DAPI-labeled allogeneic MSCs. Twelve weeks after the pig was given the MSCs, blood vessels were found within a region of generalized myocardial necrosis. In addition, MSCs were found to surround and be associated intimately with the smooth muscle layer of the blood vessels. It also was shown that the MSCs in the blood vessels expressed Factor VIII and VEGF. Factor VIII and VEGF are not expressed by cultured MSCs. The expression of such proteins by the MSCs in the blood vessels of the heart and not by MSCs in culture shows that the MSCs promote angiogenesis in the heart.

Thus, contrary to the Examiner's statements in the Office Action, Applicants have provided two working examples in which Applicants have demonstrated that MSCs repair or regenerate blood vessels of the heart and promote angiogenesis in the heart. Therefore, the specification provides sufficient information to enable one skilled in the

art to repair or regenerate blood vessels, or stimulate or promote angiogenesis in the heart of an individual by administering an effective amount of MSCs to the individual.

The Examiner also has taken the position that the specification does not provide an enabling disclosure for repairing or regenerating blood vessels or stimulating or promoting angiogenesis in the heart of an individual by administering to the individual an effective amount of MSCs from any source, including xenogeneic, or MSCs that are genetically modified.

Firstly, the claims as amended are directed to the administration of autologous or allogeneic mesenchymal stem cells. The Examiner, in the Office Action, has not stated that the administration of autologous or allogeneic mesenchymal stem cells, is not enabled.

The Examiner also states that the specification does not provide the guidance required to overcome what the Examiner calls "the art-recognized unpredictability of transplant of genetically modified MSCs."

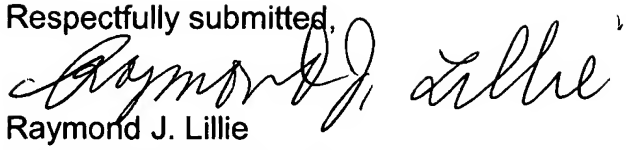
In response, Applicants note that the claims do not require that the mesenchymal stem cells be engineered genetically. As noted hereinabove, Applicants have provided working examples of administering mesenchymal stem cells in order to produce blood vessels in the heart. The Examiner is reminded that Applicants need not show that every embodiment within the scope of a claim must be operable in order for the claim to be valid. Ex parte Mark, 12 U.S.P.Q. 2d 1904 (Bd. App. Int. 1989). Therefore, Applicants clearly have proven the principle that one can administer mesenchymal stem cells to an animal in order to repair or regenerate blood vessels of the heart of the animal, or stimulate or promote angiogenesis in the heart of the animal.

To the extent that mesenchymal stem cells which were not genetically engineered had formed blood vessels in the heart, as demonstrated in Examples 6 and 7, one skilled in the art would expect reasonably that mesenchymal stem cells that were genetically engineered also would form blood vessels in the heart of an animal. Also, one skilled in the art would understand that mesenchymal stem cells could be engineered genetically by known methods such that the mesenchymal stem cells will express a desired protein of interest, such as those listed at Page 4 of the specification. Thus, one skilled in the art would expect reasonably that one could engineer mesenchymal stem cells genetically, and then administer such genetically engineered mesenchymal stem cells to an individual to repair or regenerate blood vessels in the heart of the individual or stimulate or promote angiogenesis in the heart of the individual, wherein the genetically engineered mesenchymal stem cells express the desired protein of interest. Therefore, the specification provides sufficient information to enable one skilled in the art to administer to an individual genetically engineered mesenchymal stem cells in order to repair or regenerate blood vessels in the heart or to stimulate or promote angiogenesis in the heart.

For the above reasons and others, the specification provides an enabling disclosure with respect to Claims 12 - 21, and it is therefore respectfully requested that the rejection under 35 U.S.C. 112, first paragraph, be reconsidered and withdrawn.

For the above reasons and others, this application is in condition for allowance, and it is therefore respectfully requested that the rejections be reconsidered and withdrawn and a favorable action is hereby solicited.

Respectfully submitted,



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